APPENDIX 16.1.9: DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN

PROTOCOL ZP4207-16051

The Bionic Pancreas Feasibility Trial
Testing the Bionic Pancreas with ZP4207

Investigational Product:	ZP4207
Protocol Number:	ZP4207-16051
Development Phase:	Phase 2
Sponsor:	Zealand Pharma A/S Smedeland 36 DK-2600 Glostrup (Copenhagen) Denmark Tel: +45 88 77 36 00 Fax: +45 88 77 38 98

Based on Protocol v. 7.0, 28 September 2016

SAP Version V1.0

SAP Date: December 12, 2016

[redacted]

SIGNATURE PAGE

STUDY TITLE: The Bionic Pancreas Feasibility Trial Testing the Bionic Pancreas with ZP4207

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ATC	Anatomical therapeutic class
BG	Blood glucose
BMI	Body mass index
BP	Bionic pancreas
CGM	Continuous glucose monitor
CSR	Clinical Study Report
DBR	Database review
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
MGH	Massachusetts General Hospital
RTF	Rich Text Format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
T1DM	Type 1 diabetes mellitus
VAS	Visual analog scale
WHO	World Health Organization

[redacted]

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the Zealand Pharma A/S ("Zealand") final protocol version 7.0 dated September 28, 2016. The SAP provides guidance for and description of the statistical methods and procedures to be implemented for the analyses of data collected within the scope of Clinical Trial Protocol ZP4207-16051.

Results obtained from the analysis outlined in this document will become the basis for the final Clinical Study Report (CSR) for this protocol. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Zealand and Medpace and identified in the CSR. Any minor deviations from the tables/figures/listings (provided in a separate Programming Specifications document) may not be documented in the CSR, but will be noted within the Programming Specifications document.

2. TRIAL OBJECTIVES

2.1.1 Primary Objective

The primary objective of this trial is:

- To conduct a trial testing the safety and tolerability of the bionic pancreas (BP), using either the iLet or the iPhone platform, when used with ZP4207 in 20 adult (≥18 years of age) patients with type 1 diabetes mellitus (T1DM).

2.1.2 Secondary Objective

The secondary objectives of this trial are:

- To measure glycemic regulation, including hypoglycemia exposure (percent of time spent with continuous glucose monitor [CGM] glucose < 60 mg/dL).
- To evaluate BP device reliability.
- To document the satisfaction of patients with the BP with the goal of optimizing the functionality and user interface of the BP.

3. TRIAL OVERVIEW

3.1 Overall Trial Design and Treatment Assignment

This is a Phase 2 single-center, open-label, 2-part, randomized cross-over trial in adult patients (≥18 years of age) with T1DM. Patients who already manage their T1DM using continuous subcutaneous (SC) insulin infusion pump therapy will be enrolled. The trial will assess the safety and efficacy of the BP, using either the iLet or the iPhone platform, using the glucagon analog

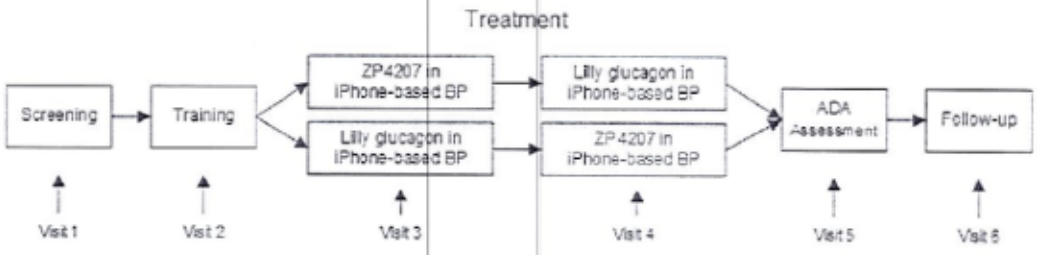
[redacted]

ZP4207 versus Lilly glucagon. In Part 1, up to 10 patients will participate in two 1-day treatment arms in random order (iPhone-based BP using ZP4207 and iPhone-based BP using Lilly glucagon) according to the randomization scheme. In Part 2, up to 10 new patients will participate in two 1-day treatment arms in random order (iLet using ZP4207 and iLet using Lilly glucagon) according to the randomization scheme. The BP will also administer insulin (insulin lispro, Lilly Humalog) using the same blood glucose (BG) control algorithm for all 4 treatment arms. The trial will be conducted at the Massachusetts General Hospital (MGH) Diabetes Center in Boston, MA. Up to 40 patients will be enrolled in this trial with the expectation that up to 10 patients will complete each part of the trial.

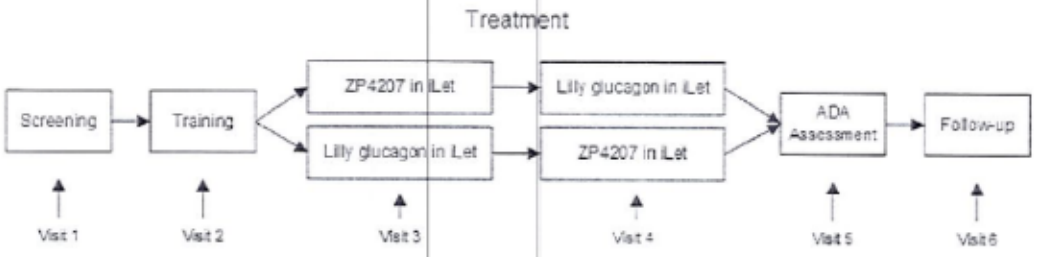
The overall trial design is displayed in Figure 1.

Figure 1. Trial Design Schematic

Part 1:



Part 2:



Patients can only participate in 1 part of the trial.
ADA = anti-drug antibodies, BP = bionic pancreas.

Patients who have completed the Screening Visit and meet all of the inclusion and none of the exclusion criteria will be enrolled. The order of the treatment visits will be randomized in blocks of 2 patients.

The schedule of events for the trial is provided in Table 1.

[redacted]

Table 1. SCHEDULE OF PROCEDURES – PARTS 1 AND 2

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 ADA Assessment Visit [6]	Visit 6 Follow-Up [7]
Informed consent	X					
Assess/confirm eligibility	X	X				
Demographics	X					
Medical, surgical, and social history; allergies	X					
Concomitant illness	X					
Concomitant medications	X	X	X	X	X	X
Height, weight, physical examination, and vital signs including body temperature and blood pressure [8]	X		X [9]	X [9]		
12-lead ECG	X		X [10]	X [10]		
Urine HCG pregnancy test and menstrual history [11]	X		X	X		
FSH [12]	X					
Screening labs – HbA1c, optional fractionated metanephrines [13]	X					
Safety lab sampling including chemistry and hematology	X		X [10]	X [10]		X
Training on devices [14]		X				
Monitored BP use			X	X		
Plasma glucose sampling [15]			X	X		
ZP4207/glucagon exposure sampling [16]			X	X		
Nausea and infusion site pain VAS and infusion site reaction Draize scale (visit start [17], hourly, & visit end)			X	X		

[redacted]

Trial Visit	Visit 1 [1] Screening	Visit 2 Training	Visit 3 [2] [3] [4] [5] (1st Treatment Visit)	Visit 4 [2] [3] [5] (2nd Treatment Visit)	Visit 5 ADA Assessment Visit [6]	Visit 6 Follow-Up [7]
Standardized lunch [18]			X	X		
In-clinic exercise [19]			X	X		
Questionnaires (pre & post BP)			X	X		
ADA			X [20]		X	X
Adverse event review			X	X	X	X

1. Once the patient has been enrolled and eligibility has been established, the order of the treatment visits will be randomized in blocks of 2 patients.
2. In Part 1, each patient will participate in 2 treatment visits: 1 with the iPhone-based BP using ZP4207 and 1 with the iPhone-based BP using Lilly glucagon in a randomized order. In Part 2, each patient will participate in 2 treatment visits: 1 with the iLet using ZP4207 and 1 with the iLet using Lilly glucagon in a randomized order. Up to 2 patients may participate in the trial per day.
3. The night before the visit, patients will place a Dexcom G4 CGM sensor in the abdominal skin and calibrate the sensor when prompted using the provided Nova StatStrip Xpress meter. Patients will be asked to arrive at the visit at least 1 hour in advance of the start of the BP having fasted since 12:00 AM the night before (treatment with simple carbohydrate of up to 30 g for a low is allowed). If the patient is not fasted, the visit will be rescheduled within the visit window. If BG is >250 mg/dL, the visit will be rescheduled within the visit window. If BG is <50 mg/dL, treatment with simple carbohydrate is allowed. If the patient experiences persistent hypoglycemia, the visit will be rescheduled within the visit window.
4. Visit 3 will take place at least 48 hours after screening (Visit 1) and no more than 30 days after screening (Visit 1).
5. There will be a 24-hour minimum washout between Visit 3 and Visit 4 and a maximum of 3 weeks between Visit 3 and Visit 4.
6. Visit 5 will take place 10 days ±3 days from Visit 4.
7. Visit 6 will take place 25 days ±4 days from Visit 4.
8. Height and physical examination will be measured at Visit 1 only.
9. Vital signs including body temperature and blood pressure will be obtained at visit start and visit end.
10. At visit start and visit end.
11. Urine HCG pregnancy test only for women of childbearing potential. The date of the last menstrual period in female patients will be obtained at Visit 1 only.
12. Test for FSH level only for postmenopausal women amenorrheic for less than 1 year.
13. If indicated by history.
14. Patients will be trained in the insertion and calibration of the Dexcom G4 sensor, diabetes management (e.g., basal insulin rate adjustment by insulin pump) during fasting prior to and between the treatment visits, and trial policies and procedures.
15. Collected at least hourly. If BG is <150 mg/dL, then sampling will be every 30 minutes. If BG is <100 mg/dL, then sampling will be every 20 minutes. If BG is <80 mg/dL, then sampling will be every 10 minutes.
16. Collected at least hourly. If BG is <150 mg/dL, more frequent samples for plasma ZP4207/glucagon may be drawn at the discretion of the Investigator.
17. Once the infusion sites have been placed but no drug has yet been administered.
18. Between approximately Hour 3 and Hour 4.
19. Between approximately Hour 6 and Hour 7.
20. Before the start of dosing.

ADA = anti-drug antibodies; BG = blood glucose; BP = bionic pancreas; CGM = continuous glucose monitor; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; VAS = visual analog scale.

[redacted]

3.2 Trial Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the safety and tolerability of ZP4207 in the BP using either the iLet or the iPhone platform as assessed by

- Number and type of adverse events (AEs)
- Clinical laboratory measurements
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Local tolerability and infusion site reactions as measured with the Draize scale
- Immunogenicity as measured by anti-drug antibodies (ADA)
- Pain as measured on a 10 cm visual analog scale (VAS)
- Nausea as measured on a 10 cm VAS

3.2.2 Secondary Endpoints

The secondary endpoints include measurements of BP function as well as glycemic and non-glycemic measurements.

3.2.2.1 Bionic Pancreas Function Endpoints

This endpoint data will be generated from the BP data during each treatment visit:

- Average percent insulin dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
    - Average percent glucagon/ZP4207 dose amounts successfully issued to the pump by the BP control algorithm that are successfully delivered by the pump
- Average percent dose amounts calculated by the BP algorithm that are successfully issued to the pump by the BP (calculated doses are not issued unless the pump is accessible and its delivery channel is available)
    - Average percent insulin dose amounts calculated by the BP control algorithm that are successfully issued by the BP
    - Average percent glucagon/ZP4207 dose amounts calculated by the BP control algorithm that are successfully issued by the BP
- Average percent of 5-minute steps during which the BP is functioning nominally in all respects based on real-time CGM data (meaning a new CGM glucose reading is captured, the dose is calculated, and the dose is issued to the pumps)
- Average percent of 5-minute steps during which the BP is functioning nominally with or without a new CGM glucose reading captured (meaning the dose is calculated and issued to the pumps). If a CGM signal is not available, the dose calculated may be based on weight or historical basal rates.
- CGM reliability index (calculated as the percent of possible values actually recorded by the CGM)

[redacted]

- CGM Mean Absolute Relative Difference versus time-stamped BG values from meter download
- List of technical faults associated with the BP including cause and resolution

3.2.2.2 Glycemic Endpoints

All of the following metrics will be generated from the Dexcom G4 Platinum CGM data during each treatment visit:

- Fraction of time spent within each of the following glucose ranges:
  - <50 mg/dL
  - <60 mg/dL
  - <70 mg/dL
  - 70-120 mg/dL
  - 70-140 mg/dL
  - 70-180 mg/dL
  - >180 mg/dL
  - >250 mg/dL
  - >300 mg/dL
- Number of severe hypoglycemic events (patients unable to self-treat, requiring the assistance of another person)
- Number of episodes of symptomatic hypoglycemia
- Number of carbohydrate interventions for hypoglycemia
- Total grams of carbohydrates taken for hypoglycemia
- Mean CGM glucose

3.2.2.3 Non-glycemic Endpoints

- Glucagon/ZP4207 total delivery per kg of body mass
- Insulin total delivery per kg of body mass
- Number of unscheduled infusion set replacements
- Number of unscheduled CGM sensor changes

4. STATISTICAL METHODOLOGY

4.1 Baseline, Endpoint, and Other Statistical Considerations

The clinical statistical analyses will be performed by Medpace.

Descriptive summary statistics including number (n), mean, median, standard deviation (SD), and range (minimum, maximum) for continuous variables (interquartile range [25th, 75th percentile] for non-parametric tests), and counts and percentages for categorical variables will be used to summarize data, as appropriate. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% significance level and 95% confidence interval, unless otherwise stated.

For all analyses, the 2 treatment arms from Part 1 (iPhone-based BP) will be compared, and the 2 treatment arms from Part 2 (iLet) will be compared. The analyses of Part 1 will be completely separate from the analyses of Part 2.

All data will be listed in patient-level data listings.

[redacted]

4.2 Analysis Populations

The following analysis populations are defined:

The Safety Analysis Set will consist of all patients who receive at least 1 dose of investigational medical product (IMP).

The Full Analysis Set (intent-to-treat population) will consist of all randomized patients. In exceptional cases, patients from the Full Analysis Set may be excluded (will be decided in the database review [DBR] meeting). In such cases, the exclusion will be justified and documented.

The Per-Protocol Set will include all patients of the Full Analysis Set who completed the trial without any major protocol violations that may interfere with the assessment of drug efficacy.

Analyses of efficacy endpoints will be based on the Full Analysis Set (and Per-Protocol Set if necessary). This decision will be made in the DBR meeting. The analysis of the safety endpoints will based on the Safety Analysis Set.

Before data are released for statistical analysis, a blinded review of all data will take place to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the analysis. Furthermore, outliers will be identified by data review according to International Conference on Harmonisation (ICH) Guidance E9.

Obviously erroneous data points may be excluded from the analyses or re-analyzed (e.g., serum concentrations). The decision to re-analyze or exclude data points from the statistical analysis is the joint responsibility of the Sponsor, the Principal Investigator, and the Trial Statistician.

The patients or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The patients and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

4.3 Subject Disposition

Subject disposition information will be summarized for each treatment sequence and for each treatment group. Counts (number and percent) of patients who are randomized, who receive the trial medication, who complete the trial, and who withdraw from the trial will be presented by treatment sequence and by treatment group. The reasons for early withdrawals will also be tabulated. The randomized patients within each treatment group will be used as the denominator for the percentage calculation. Subject disposition (including the number of screened patients and the reason for screen failure), inclusion / exclusion criteria, and comments will be listed.

The number and percent of patients in each analysis population will also be tabulated.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by treatment sequence and by treatment group for the Safety Analysis Set and repeated for the Full Analysis Set and Per Protocol Set if they are different from the Safety Analysis Set.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, body weight, and body mass index (BMI). Continuous

[redacted]

variables (e.g., age, weight, and BMI) will be summarized by descriptive statistics (n, mean, SD, minimum, median, and maximum). Categorical variables (e.g., gender, race, and ethnicity) will be summarized by the number and percentage of patients in corresponding categories.

Medical history will be summarized for the number and percentage of patients for each system organ class and preferred term by treatment group and in total. Medical and social history will also be listed.

4.5 Prior and Concomitant Medications

All medications administered during the trial will be listed and coded using the most current version of the World Health Organization (WHO) Drug Dictionary. A listing of all concomitant medications including the reported term, preferred term, and Anatomical Therapeutic Chemical (ATC) class, start and stop dates, and other relevant data will be provided. The number and percentage of patients taking prior and concomitant medications will be summarized by treatment group, ATC, and preferred term. Concomitant medications include all medications taken during the trial from screening onward. Prior medications include all medications taken and discontinued before screening.

4.6 Primary Endpoint Analyses

All safety analyses will be performed using the Safety Analysis Set. Safety variables will be summarized using descriptive statistics for continuous variables and frequency and percentage for categorical variables. These safety analyses will be compared qualitatively between the two treatment groups.

4.6.1 Adverse Events

All AEs from the time of signing the informed consent through trial completion will be recorded on the electronic Case Report Form (eCRF). An AE is any untoward medical occurrence in a clinical trial patient administered an IMP and which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (e.g., and abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP. For this trial, insulin (insulin lispro, Lilly Humalog), glucagon (glucagon for inject, Eli Lilly), and ZP4207 are all regarded as IMP.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The actual used version number will be documented in the database. Individual AEs will be presented in a listing including relationship to trial product/device, severity, and treatment period at onset. If more than 20 treatment-emergent AEs (AEs with onset after [first] dosing at Visit 3 until the follow-up Visit 6) are registered, a summary table including number of AEs, number of patients with at least 1 AE, and percentage of exposed patients with at least 1 AE will be made by system organ class and treatment period at onset. Specific by-patient listings of serious adverse events (SAEs) and treatment-emergent AEs leading to discontinuation will be provided.

[redacted]

4.6.2 Clinical Laboratory Tests

Summary statistics of clinical chemistry and hematology parameters will be provided by treatment sequence at each time point (i.e. start of visit and end of visit) within each period. Change from the start of the visit will also be summarized by treatment. Frequency counts and percentages of patients with normal and abnormal results, for parameters of interest, will also be presented by treatment sequence. Listings of patients with abnormal results will be provided.

4.6.3 Physical Examination

Physical examinations at screening will be summarized. Individual data on physical examinations will be listed.

4.6.4 Vital Signs

Vital signs (temperature, heart rate, weight, body mass index, and systolic and diastolic blood pressure) will be summarized descriptively by treatment sequence and visit time point (i.e., start of visit and end of visit) within each period. Change from the start of the visit will also be summarized by treatment group. Individual data on vital signs will be listed.

4.6.5 Electrocardiogram Findings

Electrocardiogram results will be summarized descriptively by treatment sequence and visit time point (i.e., start of visit and end of visit) within each period. Change from the start of the visit will also be summarized by treatment group. Individual data on electrocardiogram results, including Investigator's comments, will be listed.

4.6.6 Immunogenicity

Immunogenicity will be summarized descriptively by treatment sequence and visit time point along with the change from baseline to follow-up, where baseline is defined as the measurement from Visit 3 prior to IMP administration. Individual data will be listed.

4.6.7 Local Tolerability

Local tolerability and infusion site reactions will be summarized by treatment using frequency counts and percentages. Individual data, recorded with the Draize scale, regarding local tolerability and infusion site reactions will be listed.

4.6.8 Pain and Nausea

Pain and nausea will be summarized descriptively by treatment and visit time point (i.e., start of visit, hourly, and end of visit). Change from the start of the visit will also be summarized by treatment group. Individual data will be listed.

[redacted]

4.7 Secondary Endpoint Analyses

Secondary endpoint analyses will be performed on the Full Analysis Set. The same analysis will be repeated on the Per-Protocol Set, if it differs from the Full Analysis Set, to test the robustness of the analysis. All assessments will be presented by treatment group.

In general, descriptive statistics for the measurements (including percent change and/or change from baseline, if applicable) will be presented by treatment group and visit time point for all secondary endpoint variables to be analyzed. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the analysis.

4.7.1 Bionic Pancreas Function Endpoints

The plasma ZP4207/Lilly glucagon concentration will be summarized descriptively at each time point by treatment group (e.g. n, mean, SD, coefficient of variation [CV%], median, minimum, and maximum). Mean concentration will be plotted over time, by treatment group. Individual plasma concentration-time curves will be plotted by patient.

The analysis of BP function endpoints will be on an intention-to-treat basis. In cases where a treatment arm was not completed (and that arm was not repeated according to protocol criteria), available data from that arm will be used in the data analysis.

A paired t-test or the Wilcoxon signed rank test for comparison of means with normally or non-normally distributed residuals, respectively, will be used. The Shaprio-Wilk test will be used to determine the normality of the residuals for each comparison. The residuals will be obtained from an ANOVA model with treatment group as the fixed effect. If the p-value of the test is less than 0.001, the non-parametric method will be utilized to analyze the endpoint parameter. The sample SAS code for the paired t-test analysis involving the average percent of insulin dose amounts successfully delivered by the pump is included here:

```
*************************************************************************
Note: InsTrt1 = the average percent of insulin dose amount successfully
                delivered by the pump during treatment with Lilly glucagon.
      InsTrt2 = the average percent of insulin dose amount successfully
                delivered by the pump during treatment with ZP4207.
*************************************************************************;
      proc ttest ;
      paired InsTrt1*InsTrt2;
      run;
```

In a secondary analysis, any period effect and any interaction between treatment and period will be looked for, although no such interaction is predicted for the efficacy outcomes. The efficacy outcomes will be analyzed using a mixed model including terms for treatment and period as fixed effects, an interaction term, and subject nested within sequence as a random effect. A patient must have a data value for both periods in order to be included in the analysis for the given parameter. The sample SAS code for this analysis is included here:

[redacted]

```
*************************************************************************
Note: Insulin   = the average percent of insulin dose amounts successfully
                  delivered by the pump
      subject   = subject identification number.
      sequence  = sequence order (1=glucagon/ZP4207, 2=ZP4207/glucagon).
      treatment = treatment group (1=Lilly glucagon, 2=ZP4207).
      period    = analysis period number (1=Visit 3, 2=Visit 4).
*************************************************************************;
      proc mixed ;
      class subject sequence treatment period;
      model Insulin = treatment period treatment*period ;
      random subject(sequence);
      run;
```

4.7.2 Glycemic Endpoints

Similar analysis, as described previously for the BP function endpoints, will be performed for the plasma glucose measurements.

The number of patients and the proportion of patients with severe hypoglycemia events, symptomatic hypoglycemia, and carbohydrate interventions due to hypoglycemia will be summarized descriptively. The number of events will also be summarized. The proportions will be analyzed by a Fisher's exact test, if data allow. The sample SAS code for the analysis involving the proportion of subjects that had a carbohydrate intervention due to hypoglycemia is included here:

```
*************************************************************************
Note: treatment = treatment group (1=Lilly glucagon, 2=ZP4207)
      carb      = subject had a carbohydrate interventions due to
                  hypoglycemia (Yes or No).
*************************************************************************;
      proc freq ;
      tables treatment*carb / fisher ;
      run;
```

4.7.3 Non-glycemic Endpoints

The non-glycemic endpoints will be summarized descriptively by treatment group.

4.7.4 Interim Analysis

An interim database lock may occur upon completion of Part 1 of the trial to analyze the iPhone-based BP data, if applicable.

5. SAMPLE SIZE DETERMINATION

No formal sample size calculations were made. It is expected that between 20 and 24 patients will be randomized in the trial. The sample size is based on a clinical rather than statistical rationale. The sample size is considered adequate to address the primary trial objective of

[redacted]

exploring the safety of ZP4207 when used in the BP and with reference to Lilly glucagon used in the BP.

6. OTHER INFORMATION RELATED TO THE PROJECT

6.1 General Information

Medpace is responsible for the statistical analyses for this trial. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH-E9 guidelines and Medpace's biostatistical standard operating procedures (SOPs). All tables, figures, and listings will be generated with SAS® (SAS Institute Inc., Cary, North Carolina, USA) Version 9.3 or higher and printed using a Rich Text Format (RTF) file format. The program name and dates will appear in the lower left corner of all tables, figures, and listings. The last line of each page for a table or listing will be clearly marked with a solid line. This will assure the reader that text and/or data have not been lost. Footnotes (where applicable) will appear below the line at the bottom of the tables, figures, or listings and will be in paragraph format.

All tables, figures, and listings will be printed on letter size paper, 8 ½ inches by 11 inches, in landscape mode. The top margin will be 1.25 inches and other margins will be 1 inch. Generally, tables, figures, and listings will be printed using Courier New 8 pt font. This corresponds to settings in SAS of linesize=134 and pagesize=48. The format of some displays may change slightly depending on the actual length of the data displayed.

6.2 Programming Specifications

The programming specifications, including the mock-up analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents. The programming specification documents will be finalized prior to database lock.

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